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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/736,742	12/17/2003	Johann Leban	242261US0	5613

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EXAMINER	
COPPINS, JANET L	
ART UNIT	**PAPER NUMBER**
1626	

MAIL DATE	DELIVERY MODE
08/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/736,742	LEBAN ET AL.	
	Examiner	Art Unit	
	Janet L. Coppins	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-4 and 9* is/are allowed.

6)☒ Claim(s) *5-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-9 are pending in the instant application.

Response to Amendment

2. Applicants' Amendment of June 8, 2007 has been reviewed by the Examiner and entered in the file. Accordingly, claims 1 and 4 have been amended, and new claim 9 has been added. Claims 5-8 are withdrawn from consideration.

Claim Rejections - 35 USC § 112

3. Claim 4 previously rejected under 35 U.S.C. § 112, second paragraph, and 35 U.S.C. 101, as being indefinite for being drafted in terms of an "improper product-use" claim. In view of Applicants' amendment to the claim, the rejection is herein withdrawn.

Claim Rejections- 35 USC § 102

4. Claims 1-4 previously rejected under 35 U.S.C. § 102(b) as being anticipated by both Muenster et al and Katsuhira et al. In view of Applicants' amendatory changes to said claims, the rejections are withdrawn.

Rejoinder

5. Claims 1-4, drawn to products, which were previously rejected, are now found allowable over the prior art. Therefore, in accordance with MPEP 821.04 and *In re Ochiai*, claims 5-8, drawn to methods of using said products, are herein rejoined for examination.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 5 and 6 are rejected under 35 U.S.C. 112, first paragraph, as not being fully enabled. The specification, while being enabling for treating certain diseases that benefit from the inhibition of DHODH, does not reasonably provide enablement for treating all of the diseases/disorders encompassed by claims 5-6. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Regarding claim 5, while various diseases/disorders may be listed in the specification, the claims are not enabled for *all* disorders responsive to the inhibition of dihydrooratate dehydrogenase, since there is no indication as to the full range of disorders that could be treated using the instant claimed method. Regarding claim 68, the claims are not enabled for *any* and *all* acute immunological disorders, autoimmune diseases, diseases caused by malignant cell proliferation (encompasses cancer which is not enabled), or inflammatory diseases.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The specification, while being enabling for compounds according to formula (I) for treating certain diseases that respond to the inhibition of dihydrooratate dehydrogenase (DHODH), does not reasonably provide enablement for treating all of the diseases encompassed by the above claims.

Applicants are claiming a method of treating any disease or "therapeutic indication" affected by the inhibition of DHODH (claim 5), and methods of treating many unrelated diseases, including diseases that are not enabled, such as certain autoimmune diseases and cancer (claim 6).

The nature of the invention

The nature of the invention is methods of treating inflammatory, immune, and proliferative disorders/diseases, or diseases involving the DHODH pathways, comprising administering a compound to a patient in need thereof. The language of claims 5 and 6 encompasses *any* or *all* immunological or autoimmune disorders/diseases, inflammatory diseases, cancers, etc. as well as any disease capable of being treated via the inhibition of DHODH.

The state of the prior art

The state of the prior art is that dihydrooratate dehydrogenase, or DHODH, is involved in the production of lymphocytes, which play an important role in the immune response. The DHODH enzyme is known to be implicated in diseases/disorders such as inflammation, allergy, rheumatoid arthritis, GVHD, rhinitis, asthma, etc. Furthermore, "a method of treating ...acute immunological disorders [and] autoimmune diseases" encompasses many diseases, including, for example MS, AIDS/HIV, SCID, CFS, and Alzheimer's, of which there is no known cure. It is

the state of the art that there is no known treatment or prevention for Alzheimer's disease, furthermore, there are only four medications available in the United States available to temporarily slow the early stages of Alzheimer's disease. The current drugs for the treatment of Alzheimer's disease, ARICEPT®, EXELON®, REMINYL® and COGNEX®, treat early stages of Alzheimer's disease by delaying the breakdown of acetylcholine. MEMANTINE®, which blocks excess amounts of glutamate, treats late stage Alzheimer's disease. (URL:http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html).

Regarding "a method of treating... diseases caused by malignant cell proliferation," this terminology includes such varied forms of cancer or cancerous tumors as breast cancer, lung cancer, prostate cancer, malignant melanoma malignant lymphoma, colorectal cancers, bladder cancer, leukemia, etc. However, subsequent to the time of this application, as stated above, no compound is known to treat *all* cancers or *all* tumors as a blanket therapeutic.

The predictability or lack thereof in the art

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects of DHODH-mediated diseases, whether the inhibition of DHODH would affect the possible treatment of each disease listed or encompassed. The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired

pharmacological activities. In the absence of a showing of correlation between all the diseases claimed as capable of being treated by the compound of claim 1 and the inhibition of DHODH, one of skill in the art is unable to fully predict possible results from the administration of the compound of claim 1.

The amount of direction or guidance present and the presence or absence of working examples

The specification has enabled only the compounds according to formula (I) that selectively inhibit dihydrooratate dehydrogenase. Treatment of the claimed distinct disorders/diseases are normally disease or symptom oriented, thus are highly individualized, i.e. treating the symptoms of asthma (sudden recurring attacks of labored breathing, chest constriction, and coughing) would not employ the same methods as treating the symptoms of rheumatoid arthritis (stiffness and joint pain). The efficacy of an individual compound against a specific disease or symptom needs to be specifically and individually supported by factual evidence. Such evidence has not been described or supported by the specification.

The direction present in the instant specification is that the compounds of claim 1 can inhibit the production of DHODH which helps inhibit the production of lymphocytes. There are no working examples for any diseases listed in the specification. Also, the compounds which are disclosed in the specification have no pharmacological data regarding the treatment of any disease besides the inhibition of DHODH in human monocytes *in vitro*.

The specification also only discusses an *in vitro* inhibition assay on page 27 which compares the IC_{50} values of human and murine cell lines as compared with a known DHODH inhibitor, leflunomide, and provides no data for describing the efficacy of the claimed

compounds for treating the full scope of disorders that Applicants have pointed out on pages 19-22 of the specification.

The breadth of the claims

Applicants are claiming methods of treating a broad number of diseases that are unrelated. The allegation that the diseases claimed by the Applicants are all connected to the immune system or implicate the DHODH enzyme is insufficient support that the claimed compounds have specific efficacy in current available form for treating all of the diseases/disorders encompassed by the language of the claims.

The scope of claim 6 reasonably encompasses such a broad spectrum of types of "diseases caused by malignant cell proliferation" (such as cancer) that it is unreasonable to believe, on its face, that a particular chemical compound could be used for treating diseases of so many different types, in the absence of supporting scientific data or references in the disclosure to the contrary. Due to the unpredictable nature of cancer and the fact that over 3,000 different cancers exist, the various types of cancers have different causative agents, involve different cellular mechanisms, and differ in treatment protocol, thus no single compound exists presently that is known to treat *all* cancers as a blanket therapeutic. Furthermore, the Merck® manual currently has many cancer treating agents (over 12,000 compounds), yet they are only known to treat one cancer each.

The quantity of experimentation needed

The quantity of experimentation needed is undue. One of ordinary skill in the art without direction, would be unable to treat each and every disease/condition encompassed by claims 5 and 6, using the instant claimed compounds. One of skill in the art would need to determine

which diseases/disorders would be benefited by inhibiting the DHODH enzyme (claim 5) and would furthermore then have to determine whether the claimed compounds would provide treatment of all of the disorders and conditions encompassed by claim 6. Based on the unpredictable nature of the invention and the state of the prior art and the breadth of the claims, one of ordinary skill in the art would be burdened with undue "experimentation study" to determine whether the claimed compounds not only inhibit the activity of an enzyme, but also treat disorders of real-world relevance.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that " a patent is not a hunting license. It is not a reward for search , but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

Regarding claim 5, the Examiner suggests claiming the possible diseases and conditions

that are treated, rather than claiming the mechanism, which is speculative, and recommends the following language, "A method of inhibiting DHODH, for treating _____ , comprising administering to a patient in need thereof an effective amount of a compound as defined in claim 1 to the subject."

Regarding claim 6, rheumatism, diseases caused by certain viruses and Pneumocystis carinii, fibrosis, uveitis, rhinitis, asthma, and athropathy are acceptable, however the Examiner suggests further limiting the broad terminology also recited, i.e. listing specific diseases within "acute immunological disorders, autoimmune diseases, diseases caused by malignant cell proliferation, and inflammatory diseases."

9. Claim 7 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 7 provides for "The use of a compound as defined in claim 1...", but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 7 is also rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

10. Claim 8 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, see MPEP § 2172.01. Applicant has failed to include any steps involved

in the process of preparation "of a compounds as defined in claim 1." It is unclear what methods/steps Applicants are intending to recite, and one skilled in the art would not know how to prepare said compound without this information. Clarification is requested.

Conclusion

11. In conclusion, claims 1-9 are pending, claims 5-8 stand rejected, and claims 1-4 and 9 appear to be allowable over the prior art.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Coppins whose telephone number is 571.272.0680. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on 571.272.0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Janet L. Coppins
April 7, 2007

Joseph K. McKane
SPE, Art Unit 1626